
2014 Cardiovascular Risks Standing Review Panel

*Status Review for:
The Risk of Cardiac Rhythm Problems and
The Risk of Orthostatic Intolerance During Re-Exposure to Gravity*

Final Report

I. Executive Summary and Overall Evaluation

The 2014 Cardiovascular Risks Standing Review Panel (from here on referred to as the SRP) met for a site visit in Houston, TX on December 17-18, 2014. The SRP received status updates on the Risk of Cardiac Rhythm Problems (Arrhythmia Risk) and the Risk of Orthostatic Intolerance during Re-Exposure to Gravity (OI Risk).

The cardiovascular discipline lead, Dr. Michael Stenger, provided a thorough overview of progress within the past year. Based on the scientific findings shared with the SRP, it appears as though additional knowledge is needed regarding the short- and long-term effects of spaceflight on the development of cardiac rhythm problems. The SRP was unable to review the most recent International Space Station (ISS) data relevant to cardiac arrhythmias, which will be released after the conclusion of the 2014 meeting. There appears to be sufficient scientific rationale to continue studying cardiac rhythm questions under the broader risk of cardiovascular disease.

II. Comments Regarding the Risk of Cardiac Rhythm Problems (Arrhythmia) Status Review

1. *Do the non-Arrhythmia gaps and tasks in the current research plan address valid questions that still need to be answered regardless of what risk they are mapped to in the future?*

Yes, the SRP found that the non-Arrhythmia gaps and tasks in the current research plan address valid questions that still need to be answered regardless of what risk they are mapped to in the future.

2. *Are we missing anything regarding the research content for the cardiovascular system?*

1) Arrhythmia

The SRP does not believe that there was sufficient evidence presented during the 2014 meeting to conclude that arrhythmia was a very low risk. Significant study data regarding the risk of cardiac arrhythmias was not yet available for presentation. More importantly, cardiac arrhythmias by their nature present at unpredictable times, but can have devastating consequences. Furthermore, while improved screening for arrhythmia risk factors may reduce the risk of cardiac arrhythmias, the risk of clinically significant arrhythmias is not zero (Myerburg et al. Circulation 1998¹) and appropriate countermeasures such as an electrocardiogram (ECG) monitor, defibrillator and crew training need not be overly burdensome. Of note, a one pound monitor/defibrillator is currently commercially available.

During the 2014 meeting, several of the presented studies for the Arrhythmia Risk seem to suggest that a broader emphasis on spaceflight and cardiovascular disease risks may be warranted. Notably, terrestrial research shows significant long-term cardiovascular risk associated with radiation (Finch et al. *Rev Cardiovasc Med.* 2014²), stress (Steptoe et al. *Nat Rev Cardiol.* 2012³), noise (Eriksson et al. *Environ Health Perspect.* 2014⁴), and sleep disturbance (Westerlund et al. *Eur J Epidemiol.* 2013⁵) – expected environmental conditions during long-duration spaceflight. The SRP was briefed on several ongoing studies that address short- and long-term cardiovascular consequences of spaceflight. Of particular interest, the Cardio Ox study will provide longitudinal data for up to five years post-spaceflight on several key cardiovascular parameters. Since stress, endothelial damage and sleep disturbance are associated with increased blood pressure; 24-hour blood pressure measurement may provide valuable data after spaceflight.

Broadening the scope of the risk to include additional aspects of cardiovascular disease is strongly recommended. Areas of integration with other disciplines would fall under this broader cardiovascular risk, including the effects of space radiation on the development of cardiovascular disease or acceleration of existing subclinical cardiovascular disease and effects of behavioral aspects such as isolation on cardiovascular variables.

2) Exercise and Ocular Injury

During the 2014 meeting, the SRP was presented data that suggest spaceflight can lead to volume redistribution toward the eyes and visual alterations. One of the current U.S. countermeasures includes resistance training (RT) using the Advanced Resistive Exercise Device (ARED). While this countermeasure appears to be successful in counteracting bone loss and muscle atrophy, there were questions as to whether venous and intraocular pressure changes associated with exercise might be contributing to some of the visual alterations. Interestingly, it was anecdotally noted that while the U.S. program emphasizes both RT and aerobic training (AT), the Russians tend to focus more on the AT (with some RT component primarily through bands). It was also noted that the Russians deny any ocular issues, but that this is controversial, given that more recently the Russians have become engaged in the visual testing on the ISS. The SRP recommends some consideration of integrative work between the cardiovascular discipline and Bone/Muscle disciplines on this potential concern. It might be useful to look historically at prior space missions that did not have RT countermeasures and determine if visual alterations were reported. It also seems appropriate to determine what type of arterial, venous and intraocular pressures are being generated during RT in microgravity and during head-down tilt, given the fluid redistribution in space. While AT decreases intraocular pressure, RT can have a variable influence on pressure within the eye, largely depending on breathing patterns (Risner et al. *J Glaucoma.* 2009⁶). Venous pressure and middle cerebral artery blood flow during RT are largely dependent on breathing patterns, and can change greatly during the Valsalva maneuver (Pott et al. *J Appl. Physiology.* April 2003⁷). It is possible that simple countermeasures such as proper breathing patterns during RT might diminish the increased venous pressure associated with RT.

3. General Comments

Integration Studies

The SRP was asked during the 2014 meeting to address whether crossover studies among disciplines might be beneficial. There was abundant evidence that HRP groups already cooperate effectively and appear to work collegially toward common goals. A novel format that included presentations across disciplines and free time for discussion between groups led to a number of suggestions for crossover studies that could provide useful information.

The SRP discussed the importance of integrating cardiovascular assessment into some of the isolation studies being considered by the behavioral group. Isolation, depression, and psychological stress are risk factors for cardiovascular disease (Steptoe et al. *Nat Rev Cardiol.* 2012³). A three-year Mars mission would be associated with such risk factors, and it is important to consider what impact this might have on long-term cardiovascular health of these astronauts. Moreover, the concept of isolation/depression/stress on cardiovascular health is of interest to the broader community, and potential interagency announcements with the National Institutes of Health (specifically the National Heart, Lung, and Blood Institute or the National Institute on Aging) might be considered. The Antarctic isolation studies used to investigate behavioral responses to stress might also be used to measure cardiovascular changes in intima-media thickness, vascular biomarkers and blood pressure.

Radiation exposure raises the risk of cancer, but may also accelerate vascular pathology (Finch et al. *Rev Cardiovasc Med.* 2014²). Measurement of endothelial function, vascular biomarkers, vascular rigidity and intima-media thickness in experimental models used to study the incidence of cancers might inform whether there is an increased cardiovascular risk during long-duration space missions.

III. Comments regarding the Risk of Orthostatic Intolerance (OI) during Re-Exposure to Gravity Status Review

1. Are we missing anything regarding the research content for the cardiovascular system?

OI and Partial Gravity

Dr. Stenger's presentation of the progress made in the last year toward completion of the OI risk was greatly appreciated. This area is quite mature in terms of the amount of knowledge and development of countermeasures. The focus of the prior year has largely been to continue data collection of cardiovascular responses to orthostatic challenges pre- and post-flight and to test the efficacy of the gradient compression garment to prevent OI. To date, the focus has been on cardiovascular issues upon return to Earth. With the future goal of a Mars mission, however, it is not clear if OI is a significant risk when landing in partial gravity. Knowledge in this area is important, as there will be no medical support and no intravenous fluid administration post-landing in this environment. It is not clear if the gradient compression garment

currently being tested for return to Earth will be optimal for partial gravity.

Emotional Stress and OI

The Functional Task Test (FTT), which examines OI risk during 1) sit-to-stand, 2) recovery from fall-to-stand test, and 3) walk test, are likely to yield very important information towards the progress of this risk. However, the impact of emotional/mental stress on post-flight OI may be as important as physical stress. When long-duration spaceflight astronauts returned to Earth, most had OI and most had sympathetic nervous activation, which would serve to temper their OI. However, one astronaut failed to activate his sympathetic nerves, as is seen in some vaso-vagal faints (Meck et al. Psychosom Med. 2001⁸). In addition, findings of low vascular resistance in some returning astronauts with OI suggest ineffective sympathetic nervous activation and are characteristic of emotional faints (Waters et al. J Appl Physiol (1985). 2002⁹). Physical stressors such as cold and exercise usually activate the sympathetic nerves, are characterized by high blood norepinephrine levels and an increase in blood pressure. Psychological stressors are often accompanied by high blood epinephrine levels, vasodilation and sometimes by fainting (Evans et al. Auton Neurosci. 2001¹⁰). The compression garments seem to be quite successful for Earth re-entry where the post-flight tests are standard and controlled, but difficulty during re-entry to gravity would be accompanied by mental stress. The SRP suggests consideration of some emotional stressor during the FTT to determine blood pressure and heart rate changes. Integration with the behavioral group on these tests seems logical, and ground-based analogs seem appropriate.

IV. References

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V. 2014 Cardiovascular Risks SRP Status Review: Statement of Task for the Risk of Cardiac Rhythm Problems and the Risk of Orthostatic Intolerance during Re-Exposure to Gravity

The 2014 Cardiovascular Risks Standing Review Panel (SRP) will participate in a Status Review that will occur via a site visit with the Human Research Program (HRP) Chief Scientist or Deputy Chief Scientist and members of the Human Health Countermeasures (HHC) Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist or Deputy Chief Scientist on the status of NASA's current and future exploration plans and the impact these will have on the HRP.
2. Receive an update on any changes within the HRP since the 2013 SRP meeting.
3. Receive an update by the Element or Project Scientist(s) on progress since the 2013 SRP meeting.

a. The Risk of Cardiac Rhythm Problems

The Arrhythmia risk is currently under review for retirement. Since the Arrhythmia risk was created it has become a place to bookkeep other cardiovascular research related to fluid shifts or subclinical cardiovascular disease, both resulting from exposure to the spaceflight environment. NASA is currently considering the creation of a new risk to address cardiovascular disease in spaceflight OR book keeping the non-Arrhythmia cardiovascular related research in other HRP risks. Therefore, the 2014 Cardiovascular Risks SRP is not being asked to conduct a Full Research Plan Review of the Arrhythmia risk, but is being asked to address the following two points:

- i. Do the non-Arrhythmia gaps and tasks in the current research plan address valid questions that still need to be answered regardless of what risk they are mapped to in the future?
- ii. Are we missing anything regarding the research content for the cardiovascular system?

b. The Risk of Orthostatic Intolerance During Re-Exposure to Gravity

Receive an update on the Orthostatic Intolerance risk since the 2013 SRP meeting.

4. Participate in a discussion with the HRP Chief Scientist, Deputy Chief Scientist, and the Element regarding possible topics to be addressed at the next SRP meeting

The 2014 Cardiovascular Risks SRP will produce a report/comments (specifically addressing #3a above) from this status review within 30 days of the 2014 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the HHC Element that sponsors the cardiovascular discipline and also made available to the other HRP Elements. The 2014 SRP Final Report will be made available on the Human Research Roadmap public website (<http://humanresearchroadmap.nasa.gov/>).

VI. 2014 Cardiovascular Risks SRP Roster

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